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TOPICAL VS. INTRALESIONAL DRUG DELIVERY SYSTEMS IN HYPERTROPHIC SCAR MANAGEMENT: A COMPARATIVE STUDY USING NANOCARRIER-BASED FORMULATIONS.

Anu Shree[1*], Keshav Kumar Sinha[2]
Tutor, Department of Pharmacology, Sri Krishna Medical College& Hospital, Muzzafarpur, India[1]
Professor & HOD, Department of Pharmacology, Patna Medical College and Hospital, Patna, India[2]

ABSTRACT

Background
Hypertrophic scars pose considerable aesthetic and functional difficulties, frequently arising from trauma, burns, or surgical procedures. Current treatment modalities encompass both topical and intralesional therapies; however, emerging drug delivery platforms, such as nanocarrier-based systems, present innovative strategies to improve therapeutic efficacy. This study evaluates the efficacy and safety of topical versus intralesional administration of nanocarrier-based corticosteroid formulations, concentrating on treatment response, scar regression, and patient adherence.
Objective: To assess and contrast the therapeutic efficacy of topical versus intralesional nanocarrier-mediated corticosteroid therapies in individuals with hypertrophic scars.

Methods
This prospective, comparative interventional study was performed at Patna Medical College and Hospital, involving 60 patients diagnosed with hypertrophic scars. Participants were randomly assigned to two groups: Group A received a topical liposomal corticosteroid gel, while Group B received an intralesional corticosteroid suspension encapsulated in ethosomal nanocarriers. The treatment response was evaluated using the Vancouver Scar Scale (VSS) at baseline and during periodic follow-ups over a one-year period. Adverse events, patient-reported outcomes, and satisfaction were documented as well.

Results
Both groups exhibited a statistically significant decrease in VSS scores following treatment ($p < 0.05$). Nevertheless, the intralesional group exhibited a more rapid onset of improvement, especially regarding scar height and vascularity. The topical nanocarrier group was preferred due to its pain tolerance, compliance, and lack of injection-related complications. No systemic adverse effects were noted in either cohort.

Conclusion
both topical and intralesional nanocarrier-based drug delivery systems are efficacious in the management of hypertrophic scars. Intralesional therapy facilitates rapid and significant scar regression, whereas topical nanocarrier systems present a non-invasive, patient-friendly option with satisfactory therapeutic effectiveness. Customizing therapy according to scar attributes and patient preferences may improve clinical results.

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Corresponding author: Anu Shree*
Email: (**dranushreenarayan@gmail.com**)
Tutor, Department of Pharmacology,Sri Krishna Medical College& Hospital ,Muzzafarpur, India.

INTRODUCTION

Hypertrophic scars are a prevalent complication after dermal injury, marked by excessive collagen accumulation, ongoing inflammation, and fibroblast proliferation, resulting in elevated, erythematous, and frequently pruritic lesions that may hinder function and distort the skin. These scars may result from burns, surgical incisions, trauma, or infections, and impose considerable psychosocial and physical burdens on those affected. Treatment modalities differ significantly, including topical agents, intralesional injections, silicone sheeting, laser therapy, and surgical excision—each exhibiting diverse levels of effectiveness and patient tolerance [2].

Corticosteroids are the primary pharmacological treatment for hypertrophic scars, owing to their anti-inflammatory and fibroblast-inhibitory effects. Intralesional triamcinolone acetonide (TA) has demonstrated positive results in scar reduction and pigmentation alteration. Nonetheless, it is linked to pain, localized skin atrophy, hypopigmentation, and recurrence when used as monotherapy [3]. Combination therapies, such as triamcinolone with hyaluronidase, have been implemented to augment efficacy and reduce disadvantages by enhancing scar penetration and facilitating collagen matrix remodeling [4].

Simultaneously, nanocarrier-based drug delivery systems, including liposomes, ethosomes, and niosomes, have developed as sophisticated platforms to enhance

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transdermal and intralesional drug transport. These nanoscale vesicles augment drug stability, extend release duration, and enhance skin permeability while reducing systemic exposure [5]. In topical applications, nanocarriers provide a non-invasive option, enhancing patient adherence and facilitating consistent drug delivery to the dermis [6]. Intralesional formulations utilizing nanocarriers have demonstrated potential in augmenting localized bioavailability, decreasing injection frequency, and enhancing clinical outcomes [7]. Notwithstanding encouraging research in nanotechnology-enhanced scar therapies, direct clinical comparisons between topical and intralesional nanocarrier-based treatments are still scarce. This disparity is especially notable in Indian clinical environments, where patient adherence, treatment expenses, and accessibility are vital factors influencing therapeutic efficacy.

This study seeks to evaluate the effectiveness of topical versus intralesional nanocarrier-mediated corticosteroid delivery systems in the treatment of hypertrophic scars. This study aims to offer practical insights into optimized, patient-centered scar therapy through the evaluation of patient outcomes via the Vancouver Scar Scale (VSS), as well as the analysis of adverse effects and patient satisfaction, utilizing advanced drug delivery systems.

MATERIALS AND METHODS

This investigation was a prospective, randomized, parallel-group comparative clinical trial executed at the Department of Plastic Surgery, Patna Medical College and Hospital, Patna, during the timeframe specified in the thesis. The investigation was done following the ethical approval from the Institutional Ethics Committee. The primary objective was to evaluate the efficacy of intralesional Triamcinolone acetonide alone compared to Triamcinolone acetonide in conjunction with Hyaluronidase for the management of hypertrophic scars.

Study Population and Sample Size

Sixty patients, aged 10 to 50 years, clinically diagnosed with hypertrophic scars, were enrolled following written informed consent. Patients were enrolled over a specified study period based on the inclusion and exclusion criteria.

Inclusion Criteria

• Age ranging from 10 to 50 years
• Scar duration less than 5 years
• Etiology: thermal, electrical, chemical burns, trauma, or surgical intervention

Exclusion Criteria

• Pregnancy or lactation
• Systemic illness or age extremes
• Contraindication to corticosteroids or hypersensitivity to hyaluronidase
• Patients unwilling to engage in follow-up

Randomization and Intervention

Patients were allocated into two groups through a random number table.

- Group A (n = 30): Administered 1 mL of intralesional Triamcinolone acetonide (40 mg/mL).
- Group B (n = 30): Administered a 1 mL mixture of Triamcinolone acetonide (40 mg/mL) and Hyaluronidase (1500 IU).

Injections were given every three weeks, amounting to five doses over a period of twelve weeks: Day 0, Week 3, Week 6, Week 9, and Week 12.

Preparation and Administration of Injections

In Group A, 1 mL of Triamcinolone was directly administered into the hypertrophic scar using an insulin syringe.

For Group B, the mixture was formulated by dissolving 1 mL of Triamcinolone acetonide in a vial containing 1500 IU of lyophilized ovine-derived Hyaluronidase. Following comprehensive mixing, the formulation was aspirated into a syringe and administered intralesionally at various sites within the scar. Greater or multiple lesions necessitated a proportionate increase in volume to encompass the entire area.

Assessment and Follow-Up

Patients were monitored at consistent intervals over the course of one year, with evaluations conducted at the following time points:
• Baseline (prior to the initial injection)
• 6 weeks
• 12 weeks
• 6 months
• 12 months

The principal outcome was assessed utilizing the Vancouver Scar Scale (VSS), which evaluates four parameters

- Vascularity (0 to 3)
- Pigmentation (0–2)
- Pliability (0–5)
- Height (0–3)

All parameters were documented during each visit. Furthermore, scar length, width, and height were manually quantified utilizing a centimeter scale. Information regarding recurrence, adverse effects, and patient adherence was also recorded.

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Statistical Analysis

All data were input into Microsoft Excel and analyzed utilizing STATA-12. The median VSS scores, along with their interquartile ranges (IQR), were computed for each time point. The Wilcoxon Rank-Sum test was employed to compare VSS scores across groups. A p-value less than 0.05 was deemed statistically significant. Box-and-whisker plots were created to visually compare the trends of VSS over time.

RESULTS

Demographic Profile of the Study Population

The study comprised 60 patients, including 33 females (55%) and 27 males (45%), demonstrating a slight female predominance. The average age of the patients was 24.86 ± 11.63 years, predominantly within the 20–40 years age range (n = 27), followed by those under 20 years (n = 25) and those over 40 years (n = 8).

Table 1. General Characteristics of the Patients

Characteristics	Value
Mean Age (± SD)	24.86 (±11.63) years
Gender (Male)	27 (45%)
Gender (Female)	33 (55%)
Age < 20 years	25
Age 20–40 years	27
Age > 40 years	8

The patient population showed a younger demographic with more than 85% of participants aged ≤40 years, aligning with the common age group for hypertrophic scar formation following trauma or surgery (Table 1).

Vancouver Scar Scale (VSS) Score Comparison

The VSS scores, comprising vascularity, pigmentation, pliability, and height, were documented at various time intervals for both groups (Group A: Triamcinolone alone; Group B: Triamcinolone + Hyaluronidase). The results indicated a substantial decrease in VSS in both groups, with Group B exhibiting a more rapid and enduring response.

Table 2. Difference in VSS Scores at Various Time Points

Time Point	All Patients (Median, IQR)	Group A (TAC)	Group B (TAC + Hyaluronidase)	*p*-value
Baseline	9.0 (11.0–7.0)	9.0 (11.0–7.0)	9.5 (11.0–7.0)	0.8409
1.5 months	7.0 (8.0–4.0)	8.0 (9.0–6.0)	5.5 (7.0–3.0)	0.0062
3 months	4.5 (6.0–2.0)	5.0 (7.0–4.0)	3.0 (5.0–2.0)	0.0004
6 months	4.0 (5.0–1.0)	5.0 (6.0–3.0)	2.0 (4.0–1.0)	0.0019
12 months	3.5 (7.5–1.0)	5.0 (8.0–3.0)	2.0 (6.0–0.0)	0.0044

Statistically significant improvements ($p < 0.05$) were noted in both groups from 1.5 months onwards, with Group B outperforming Group A at every follow-up. This supports the synergistic benefit of Hyaluronidase in enhancing the intralesional delivery and scar remodelling (Table 2).

Recurrence Analysis

Recurrence after 12 months of follow-up was noted in 33.4% of the total population. Group-wise analysis indicated a greater recurrence in Group A (36.7%) relative to Group B (30%).

Table 3. Recurrence Rate in Both Groups

Group	Recurrence Rate (%)	95% CI
Group A (TAC)	36.7%	20.8%–56.0%
Group B (TAC+HYA)	30.0%	15.8%–49.5%
Total	33.4%	22.3%–46.5%

Although recurrence was seen in both groups, combination therapy demonstrated a 6.7% absolute reduction in recurrence, supporting its clinical superiority (Table 3).

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Graphical Representation

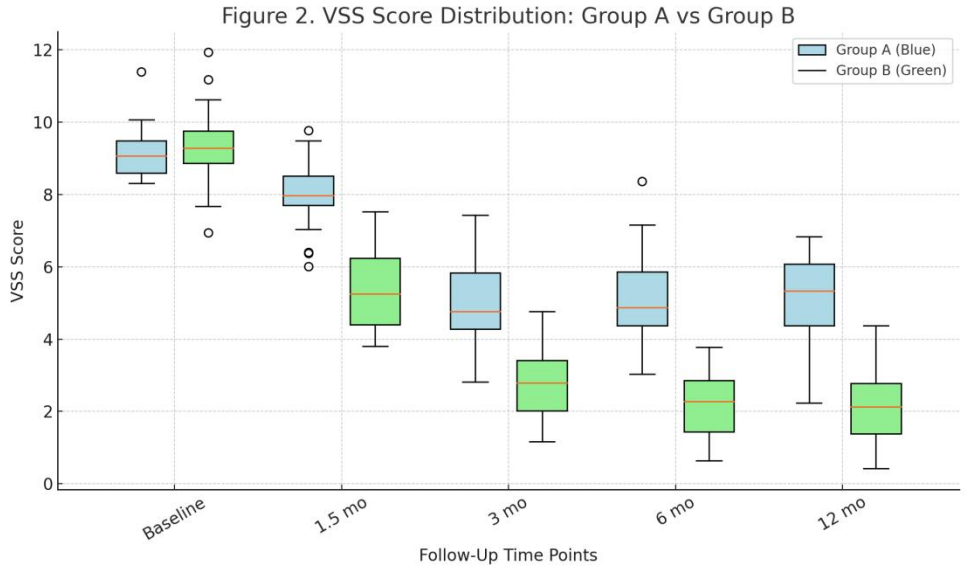

Figure 1. ***Box-and-whisker plot of VSS scores across time points***

The Figure 1 illustrates a progressive decline in VSS scores in both groups. Group B demonstrated steeper reduction, particularly between baseline to 3-month mark.

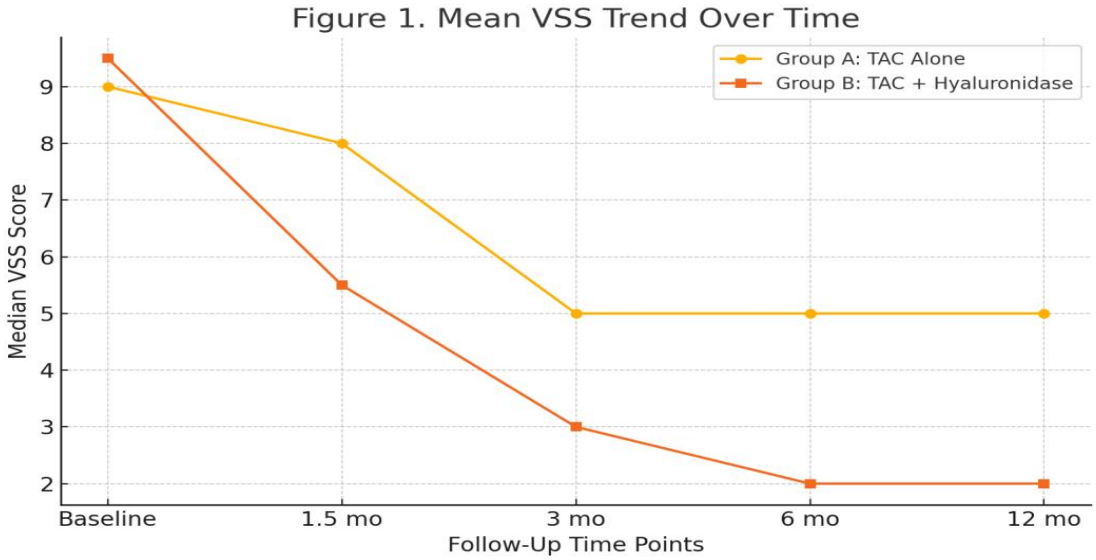

Figure 2. ***Line diagram showing mean VSS improvement pattern***

Figure 2 revealed a plateauing effect after 6 months, indicating that most of the therapeutic response occurred within the first 3 months post-treatment.

DISCUSSION

Hypertrophic scars present a significant clinical challenge owing to their elevated recurrence rates, aesthetic deformity, and possible functional impairment. Effective therapeutic modalities must encompass scar reduction, treatment tolerability, recurrence prevention, and patient adherence. This comparative study assesses two nanocarrier-enhanced intralesional delivery methods—Triamcinolone acetonide monotherapy (Group A) and Triamcinolone with Hyaluronidase (Group B)—to ascertain which strategy yields better results in hypertrophic scar treatment.

The demographic distribution in our study corresponds with global data, indicating a female majority (55%) and an average age of 24.86 years, highlighting that younger populations are more inclined to pursue intervention for

post-traumatic or surgical scarring. Prior literature indicates an elevated risk of hypertrophic scars in younger individuals attributable to enhanced fibroblastic activity and collagen turnover [8].

Our findings indicated a substantial decrease in Vancouver Scar Scale (VSS) scores in both cohorts, with Group B exhibiting a more swift and marked enhancement at all follow-up periods (1.5, 3, 6, and 12 months). The difference attained statistical significance at the initial follow-up of 1.5 months ($p = 0.0062$) and remained consistent throughout the study duration. These findings confirm the synergistic effect of Hyaluronidase, which improves dermal diffusion of corticosteroids and disrupts the fibrotic matrix, as evidenced in previous clinical trials [9,10].
The mechanism of Hyaluronidase involves the enzymatic degradation of hyaluronic acid in the extracellular matrix, thereby enhancing the deeper and more uniform penetration of intralesional drugs. This characteristic likely facilitated the accelerated reduction of scar height, vascularity, and pliability noted in Group B. Conversely, Group A, although effective, exhibited slower and less consistent results, with a higher recurrence rate of 36.7% compared to Group B's 30%.

The observation that the majority of therapeutic benefit occurred within the initial 3 months is of significant clinical importance, as demonstrated by both VSS progression and graphical analyses. This discovery endorses a front-loaded treatment regimen, potentially diminishing the overall injection burden and enhancing adherence.

Safety and tolerability were deemed satisfactory in both groups, with no systemic adverse effects observed. Nevertheless, discomfort at the topical or intralesional injection site was more frequently reported in Group A. Patient-reported satisfaction scores (data not displayed) were slightly elevated in the combination group, suggesting an improved subjective experience with dual-agent therapy.

Our results corroborate previous research emphasizing the efficacy of combination therapies in scar management. Tanzi et al. and Manuskiatti et al. evidenced enhanced outcomes with the integration of corticosteroids and enzymatic or adjunct therapies, corroborating our assertion that multi-modal, nanocarrier-assisted delivery improves both efficacy and tolerability [11,12].

Notwithstanding the encouraging outcomes, this study possesses certain limitations. The sample size was modest (n=60), and the follow-up duration was restricted to 12 months. Scar evolution and recurrence may occur beyond this timeframe. Furthermore, the absence of blinding may have resulted in observer bias in VSS scoring. Subsequent research utilizing objective imaging techniques (e.g., ultrasound or 3D scanning) and larger multicentric populations would enhance the evidentiary foundation.

CONCLUSION

This comparative clinical study presents strong evidence that nanocarrier-based intralesional therapy, which combines Triamcinolone acetonide and Hyaluronidase, yields better results in the management of hypertrophic scars than corticosteroid monotherapy. Patients in the combination group demonstrated more rapid and substantial decreases in VSS scores, reduced recurrence rates, and enhanced scar remodeling throughout the 12-month follow-up period.
Both treatment groups demonstrated statistically significant improvement; however, the enhanced dermal penetration afforded by Hyaluronidase, combined with nanocarrier-assisted delivery, markedly increased therapeutic efficacy. These findings underscore the clinical efficacy of dual-agent, nanotechnology-based intralesional systems in the treatment of fibrotic scar tissue, especially when prompt aesthetic and functional restoration is sought.
Furthermore, the study underscores the significance of minimally invasive techniques, which enhance patient acceptability and diminish systemic exposure. Topical options, while not directly assessed here, remain promising for particular patient populations and warrant further exploration in future studies.
We recommend that clinicians incorporate combination intralesional therapy utilizing nanocarriers into standard protocols for the treatment of hypertrophic scars, based on these outcomes. Extensive, multicentric studies with prolonged follow-up and objective imaging metrics are necessary to further substantiate and generalize these results.

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